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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Dosuk D. Lee et al.	Art Unit:	1617
Serial No.:	09/693,120	Examiner:	Shahnam J. Sharareh
Filed:	October 20, 2000	Customer No.:	21559
Title:	CHEMOTHERAPEUTIC COMPOSITION USING NANOCRYSTALLINE CALCIUM PHOSPHATE PASTE		

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Commissioner for Patents
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APPELLANTS' BRIEF ON APPEAL
SUBMITTED PURSUANT TO 37 C.F.R. § 1.192

In support of Appellants' Notice of Appeal that was filed in connection with the above-captioned case on November 20, 2003, and with reference to the final Office Action that was mailed in this case on May 21, 2003 and the Advisory Action that was mailed in this case on November 26, 2003, submitted herewith in triplicate is Appellants' brief on appeal.

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Real Party in Interest

The real party in interest in this case is Etex Corporation, to whom all interest in the present application has been assigned by virtue of an Assignment filed with the U.S. Patent and Trademark Office.

Related Appeals and Interferences

Two related applications, U.S. Serial No. 09/569,081 and U.S. Serial No. 09/692,664, are on appeal. There are currently no pending interferences related to this case.

Status of Claims

Claims 22-44 are pending in this application.

Claims 22-44 were finally rejected in a final Office Action mailed on May 21, 2003, and are appealed.

Status of Amendments

An amendment was filed on October 15, 2003 in connection with a reply to the final Office Action mailed on May 21, 2003. This amendment was entered, as is indicated in the Advisory Action mailed on November 26, 2003, and the present appeal is based on the claims as amended (as reproduced in Appendix 1).

Summary of the Invention

The invention features an anticancer composition containing a mixture of an anticancer

agent and a calcium phosphate paste (see, e.g., page 5, line 2, through page 9, line 2, of the specification). The calcium phosphate paste is formed by combining one or more nanocrystalline or poorly crystalline calcium phosphates with a physiologically acceptable fluid. The paste, when formed, exhibits an injectable or formable consistency at the time of administration, and is hardenable at the tumor site. The invention also features a kit for preparing a flowable anticancer composition (see, e.g., page 9, lines 3-11, of the specification).

Issue

The issue on appeal is whether the Examiner erred in rejecting claims 22-44 under 35 U.S.C. § 103(a) for obviousness over Yamamura et al. (Japanese Journal of Pharmacology 65:289-291, 1994; hereinafter "Yamamura") in view of Gerhart et al. (U.S. Patent No. 5,085,861; hereinafter "Gerhart") and Constantz et al. (U.S. Patent No. 5,782,971; hereinafter "Constantz").

Claims 22-44 were also provisionally rejected for obviousness-type double patenting over claims 22-44 of copending U.S. Serial No. 09/692,664. Appellants request that the provisional obviousness-type double patenting rejection be held in abeyance until allowable subject matter has been determined. At that time, Appellants will, if necessary, submit a terminal disclaimer to overcome this rejection.

Grouping of Claims

The claims stand or fall together.

Argument

Claims 22-44 were finally rejected under 35 U.S.C. § 103(a) for obviousness over Yamamura in view of Gerhart and Constantz. The Examiner states:

> Yamamura discloses methods of implanting injectable doxorubicin loaded hydroxyapatite beads for treating tumor...Gerhard discloses calcium phosphate containing compositions comprising biocompatible calcium phosphate ceramics that can be in the form of an injectable or moldable paste and will solidify within 10 minutes after administration...Constanz et al. teach amorphous calcium phosphate containing compositions that are used as suitable drug delivery vehicles...Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to modify physical characteristics of Yamamura's composition into an injectable paste, as suggested by Gerhard and Constanz, and formulate a hardenable calcium phosphate formulation that is easily administered to a site of interest such as a tumor... (Final Office Action dated June 4, 2003, pp. 3-4.)

This rejection is in error and should be reversed.

The Legal Standard for Obviousness under 35 U.S.C. § 103

To establish a *prima facie* case of obviousness under § 103, the Examiner must demonstrate that the differences between the claimed invention and the prior art are such that the subject matter as a whole would have been obvious, at the time the invention was made, to a person having ordinary skill in the art. See 35 U.S.C. § 103(a) (Supp. III 1997); *In re Dembiczak*, 175 F.3d 994, 998, 50 USPQ2d 1614, 1616 (Fed. Cir. 1999). Whether or not a claimed invention is obvious is a legal conclusion based on underlying factual inquiries, including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness. *Id.*

Importantly, where "claimed subject matter has been rejected as obvious in view of a combination of references, a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should . . . carry out the claimed process; and (2) whether the prior art would have revealed that in so . . . carrying out, those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Furthermore, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chem. Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). As the Federal Circuit recently observed:

> A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. . . . Most if not all inventions arise from a combination of old elements. . . . Thus, every element of a claimed invention may often be found in the prior art. . . . However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. . . . Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, *there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant.*

In re Kotzab, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000)(emphasis added)(citations omitted). The evidence of a suggestion, teaching, or motivation to combine "must be clear and particular." *Dembiczak*, 175 F.3d at 999. "Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness." *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 880, 45 USPQ2d 1977, 1981 (Fed. Cir. 1998). "Broad conclusory statements regarding the teaching of multiple

references, standing alone, are not 'evidence.'" *Id.*

Thus, the case law clearly mandates that, even if the Examiner identifies every element of a claimed invention in various pieces of the prior art, this alone is insufficient to negate patentability. Otherwise, "rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention." *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998). To avoid hindsight based on the invention to defeat patentability of the invention, the Federal Circuit requires an Examiner to show a motivation to combine the references that create the case of obviousness. *Id.* That is, "the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *Id*; emphasis added.

Claims 22-44 are Not Obvious Over Yamamura, Gerhart, and Constantz

Claims 22-44 were rejected under 35 U.S.C. § 103(a) for obviousness over the combination of Yamamura, Gerhart, and Constantz. The Examiner has merely identified each element of the present claims in the cited art, but has failed to demonstrate that the cited references teach, suggest, or motivate the skilled artisan to combine their reference teachings to yield the invention of claims 22-44. Appellants will first discuss the rejection as it applies to claims 22-41.

Yamamura discloses implanting a single adriamycin (ADR; i.e., doxorubicin)-loaded

hydroxyapatite (HAP) bead directly into the central portion of a chondrosarcoma tumor present in a Sprague-Dawley rat (see page 289, col. 2, line 12, and page 290, col. 1, lines 16-18). The Examiner acknowledges that Yamamura fails to teach or suggest all of the limitations of claims 22-41, stating "Yamamura does not specifically teach a paste formulation" (Final Office Action, p. 3). To remedy the deficiencies of Yamamura, the Examiner cites Gerhart and Constantz. These references fail to teach or suggest a composition containing a calcium phosphate paste in combination with an anticancer agent, as is recited in claims 22-41. Therefore, as is discussed below, Gerhart and Constantz fail to provide the necessary teaching, suggestion, or motivation to combine their reference teachings with Yamamura to yield the invention of claims 22-41.

The Examiner relies on Gerhart and Constantz to provide the claim limitations missing in Yamamura. But, like Yamamura, neither Gerhart nor Constantz teaches or suggests combining a calcium phosphate paste with an anticancer agent.

Gerhart discloses a "bone cement...comprised of a particulate biocompatible calcium phosphate ceramic and particulate resorbable calcium salt dispersed in a cross-linked biodegradable polyester matrix...[that can be] used for bone/implant fixation, or as a filler or cement for bone repair" (see the Abstract). Gerhart also discloses that an antibiotic can be incorporated into the cross-linked biodegradable matrix (col. 4, lines 30-34, and col. 10, lines 48-54). Gerhart does not teach or suggest the incorporation of an anticancer agent into the bone cement.

The Examiner states that "Gerhart's compositions contain active agents that are readily used in treatment of cancers such as bone tumor" (Final Office Action, p. 4). This is incorrect. Gerhart merely discloses a bone cement containing an antibiotic that is employed to fill bone

cavities that remain following the excision of tumor-containing bone (see col. 13, lines 45-49). Gerhart fails to teach or suggest that the bone cement contains any agent that would be used to treat the tumor itself, and certainly not an anticancer agent, as is recited in claims 22-41. The American Heritage Dictionary clearly defines an antibiotic as a "substance, such as penicillin or streptomycin, produced by or derived from certain fungi, bacteria, and other organisms, that can destroy or inhibit the growth of other microorganisms" (The American Heritage® Dictionary of the English Language, Fourth Edition, 2000; emphasis added). Because an antibiotic would be understood by one skilled in the art to be a substance that destroys or inhibits the growth of microorganisms, not a substance that has the ability to destroy or inhibit eukaryotic cancer cells, Gerhart would fail to provide any motivation to prepare a bone cement containing an anticancer. Therefore, Gerhart cannot be relied upon as providing the motivation, which is absent in Yamamura, to prepare a calcium phosphate paste composition containing an anticancer agent.

Constantz also fails to provide this motivation. Constantz merely discloses a calcium phosphate cement composition that may contain, for example, an antibiotic or a protein (see, e.g., col. 5, line 57, though col. 6, line 11). Constantz lacks any teaching or suggestion that the protein is an anticancer agent, or that an anticancer agent should be combined with the calcium phosphate cement composition, as is acknowledged by the Examiner (see the final Office Action, page 5).

Gerhart and Constantz, alone or in combination, fail to teach or suggest combining an anticancer agent with a calcium phosphate paste, while Yamamura, which discloses a hydroxyapatite bead in combination with an anticancer agent, adriamycin, fails to teach or suggest substituting the bead formulation with any other formulation, such as a paste

formulation. The skilled artisan would not be motivated to combine Gerhart and Constantz with Yamamura because none of the references teaches or suggests the desirability of such a combination, as is required (see, *In re Kotzab*, *supra*).

The M.P.E.P. § 2143.01 states:

> Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." (Citations omitted.)

Furthermore:

> A statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made'" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). See also *In re Kotzab,* 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000).

The Examiner relies upon Gerhart and Constantz to provide support for the modification of Yamamura to yield the invention recited in claims 22-41. Neither Gerhart or Constantz teaches or suggests a composition containing a calcium phosphate paste in combination with an anticancer agent, nor do they provide any motivation to modify Yamamura to provide a paste formulation for the ADR-loaded HAP bead.

Yamamura discloses the use of an ADR-loaded HAP bead, but fails to teach or suggest that the HAP bead could be provided in any other form (e.g., as a calcium phosphate paste).

Gerhart and Constantz do not provide the necessary motivation to modify Yamamura's HAP bead to yield the presently claimed calcium phosphate paste composition, because Gerhart and Constantz merely disclose the use of a calcium phosphate cement composition that contains an antibiotic or, as is also disclosed in Constantz, a protein. Neither of the cited references explicitly or implicitly teaches or suggests that an anticancer agent could be used in place of the antibiotic/antimicrobial agent. Absent this disclosure, the skilled artisan would have no motivation to modify Yamamura based on Gerhart and Constantz to yield the invention of claims 22-41 (M.P.E.P. § 2143.01, *supra*). Furthermore, the mere fact that the references can be combined or modified does not render the resultant combination obvious unless the prior art references also suggest the desirability of the combination, which they do not (*In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)).

Therefore, the Examiner has simply identified each element of claims 22-41 and has argued that because all of the elements are present in the cited references, a *prima facie* case of obviousness has been established (see, e.g., p. 2 of the Advisory Action). This is clearly impermissible where the references do not provide an objective reason for combining reference teachings (see, e.g., M.P.E.P. § 2143.01, *supra*), as occurs in the present situation. For all of the reasons provided above, Appellants respectfully request that the rejection of claims 22-41 under 35 U.S.C. § 103(a) over Yamamura, Gerhart, and Constantz should be reversed.

The Suggestion to Combine the Cited References and the Expectation of Success is Found Solely in Appellants' Disclosure

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the prior art must

suggest the claimed combination and provide a reasonable expectation of success; these elements cannot be found solely in Appellants' disclosure (see *In re Vaeck, supra*, and *In re Dow Chem. Co., supra*). As is discussed above, Yamamura fails to teach or suggest combining an anticancer agent with a calcium phosphate paste, and Gerhart and Constantz fail to provide any teaching, suggestion, or motivation to combine their calcium phosphate cement compositions with the Yamamura bead composition to yield the composition recited in claims 22-41. The Examiner has not established a clear motivation provided solely from the cited references that would guide the skilled artisan to combine the reference teachings to yield the invention recited in claims 22-41 prior to the disclosure of Appellants' present invention, nor any expectation of success other than that derived from the teachings of Appellants' disclosure. Therefore, both the motivation to combine the cited references and the reasonable expectation of success must be derived solely from the teachings of Appellants' disclosure.

Use of Appellants' disclosure to provide a motivation for combining the cited references and to derive a reasonable expectation of success is an improper use of hindsight and cannot form the basis for an obviousness rejection. The Federal Circuit has repeatedly cautioned against the "insidious effects of hindsight" in making obviousness determinations. *Life Technologies, Inc. v. Clontech Labs, Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000). More specifically, the court has stated:

> it is impermissible to first ascertain factually what [Applicants] did and then view the prior art in such a manner as to select from the random facts of art only those which may be modified and then utilized to reconstruct appellants invention from such prior art. (*Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985).)

To avoid the use of hindsight, the M.P.E.P. has adopted the same view, stating that "the mere

fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness," and that the art must provide "an objective reason to combine the teachings." M.P.E.P. § 2143.01, *supra*. Further, a generally high level of skill in the art cannot be relied upon to provide such a reason. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308 (Fed. Cir. 1999). Thus, absent a specific motivation to combine references, a *prima facie* case of obviousness cannot be made.

Because the prior art does not teach, suggest, or motivate the skilled artisan to prepare the composition of claims 22-41, and because the cited references fail to provide a reasonable expectation of success for making or using such a composition, absent the guidance provided by Appellants' disclosure, Appellants respectfully submit that the Examiner has relied upon improper hindsight to form the basis for the rejection of claims 22-41 for obviousness. Therefore, Appellants respectfully request that for this reason as well, the rejection of claims 22-41 under 35 U.S.C. § 103(a) over Yamamura, Gerhart, and Constantz should be reversed.

Claims 42-44 are Not Obvious in View of Yamamura in Combination with Gerhart and Constantz

Claims 42-44 were also rejected under 35 U.S.C. § 103(a) over Yamamura in combination with Gerhart and Constantz. The Examiner states that, based on the combination of Yamamura, Gerhart, and Constantz, "the ordinary artisan would have had a reasonable expectation of success in preparing a ready to use kit for easing the access and use of such compositions at a clinical setting" (Final Office Action, p. 5). Appellants respectfully request reversal of this rejection as well.

As is discussed above, Yamamura, Gerhart, and Constantz fail to provide any motivation to prepare a calcium phosphate paste containing an anticancer agent; the Examiner has simply identified all of these elements in the cited references. Because the cited references fail to provide the necessary motivation to prepare a composition containing a calcium phosphate paste and an anticancer agent, as is recited in claims 22-41, the cited references also cannot be relied upon to provide the necessary motivation to prepare a ready to use kit containing such a composition, as is recited in claims 42-44. For this reason, a *prima facie* case of obviousness cannot be established

Furthermore, as is discussed above with respect to claim 22, and claims dependent therefrom, the expectation of success for preparing a calcium phosphate paste containing an anticancer agent is found solely in Appellants' disclosure, not in the combined disclosures of Yamamura, Gerhart, and Constantz. The Examiner has merely relied upon hindsight to provide a motivation for combining the cited references and to establish a *prima facie* case of obviousness against claims 42-44, which is improper (see, e.g., *Interconnect Planning Corp. v. Feil, supra*). Because the prior art does not teach, suggest, or motivate the skilled artisan to prepare a ready to use kit containing the ingredients necessary to prepare a composition containing a calcium phosphate paste in combination with an anticancer agent, and because the cited references fail to provide a reasonable expectation of success for preparing such a kit, Appellants respectfully submit that the rejection of claims 42-44 under 35 U.S.C. § 103(a) over Yamamura, Gerhart, and Constantz should also be reversed.

CONCLUSION

Appellants respectfully request that the rejection of claims 22-44 be reversed. Enclosed is a check for $165.00 in payment of the fee required by 37 C.F.R. § 1.17(c). Also enclosed is a petition to extend the period for replying for five months, to and including June 20, 2004, and a check for the fee required by 37 C.F.R. § 1.17(a).

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: June 16, 2004

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Appendix of Claims on Appeal

1-21 (Cancelled)

22. (Previously Presented) An anticancer composition comprising a mixture of an anticancer agent and a calcium phosphate paste, said paste comprised of one or more nanocrystalline or poorly crystalline calcium phosphates and a physiologically acceptable fluid, the paste having an injectable or formable consistency at the time of administration and hardenable at the tumor site.

23. (Original) The composition of claim 22, wherein each calcium phosphate has a Ca/P ratio of less than or equal to 1.7.

24. (Previously Presented) The composition of claim 22, wherein the anticancer agent is selected from the group consisting of methotrexate, cisplatin, prednisone, hydroxyprogesterone, medroxyprogesterone acetate, megestrol acetate, diethylstilbestrol, testosterone propionate, fluoxymesterone, vinblastine, vincristine, vindesine, daunorubicin, doxorubicin, hydroxyurea, procarbazine, aminoglutethimide, mechlorethamine, cyclophosphamide, melphalan, uracil mustard, chlorambucil, busulfan, carmustine, lomustine, dacarbazine (DTIC, dimethyltriazenomideazolecarboxamide), procarbozine, 5-fluorouracil, cytarabine, cytosine arabinoside, 6-mercaptopurine, tamoxifen, paclitaxel, etoposide, vinorelbine, gemcitabine, leuprolide, flutamide, goserelin acetate, thioguanine, and mixtures thereof.

25. (Original) The composition of claim 22, wherein the anticancer composition is of a consistency administrable to the tumor site by cannula or by injection.

26. (Original) The composition of claim 22, wherein the nanocrystalline or poorly crystalline calcium phosphate cement comprises a calcium phosphate selected from the group consisting of amorphous calcium phosphate, poorly crystalline apatitic (PCA) calcium phosphates (PCA), dicalcium phosphates, such as dicalcium phosphate dihydrate (DCPD) and dicalcium phosphate anhydrous (DCPA), tricalcium phosphates (TCP), monetite, monocalcium phosphate monohydrate (MCPM), hetpacalcium phosphate, calcium pyrophosphate, calcium metaphosphate, octacalcium phosphates (OCP), hydroxyapatites (HA).

27. (Original) The composition of claim 26, wherein at least one of the nanocrystalline or poorly crystalline calcium phosphates is selected from the group consisting of amorphous calcium phosphate and poorly crystalline apatitic calcium phosphate.

28. (Original) The composition of claim 22, wherein each of the said one or more nanocrystalline or poorly crystalline calcium phosphates has a calcium to phosphate ratio in the range of 1.3 to 1.67.

29. (Original) The composition of claim 22, wherein the nanocrystalline or poorly crystalline calcium phosphate paste has an overall calcium to phosphate ratio in the range of 1.0 to 1.7.

30. (Original) The composition of claim 22, wherein the nanocrystalline or poorly crystalline calcium phosphate paste has an overall calcium to phosphate ratio in the range of 1.0 to 1.67.

31. (Original) The composition of claim 22, wherein the nanocrystalline or poorly crystalline calcium phosphate paste has an overall calcium to phosphate ratio in the range of 1.40 to 1.65.

32. (Original) The composition of claim 22, wherein nanocrystalline or poorly crystalline calcium phosphate paste comprises a physiologically acceptable fluid in an amount sufficient to produce a paste having injectable or formable consistency for at least five minutes.

33. (Original) The composition of claim 22, wherein nanocrystalline or poorly crystalline calcium phosphate paste comprises a physiologically acceptable fluid in an amount sufficient to produce a paste having injectable or formable consistency for at least twenty minutes.

34. (Original) The composition of claim 22, wherein the nanocrystalline or poorly crystalline calcium phosphate paste is hardenable into an apatitic calcium phosphate.

35. (Original) The composition of claim 22, wherein a therapeutically effect amount of anticancer agent is released from the composition for a time greater than one week.

36. (Previously Presented) The composition of claim 22, wherein a therapeutically effect amount of anticancer agent is released from the composition for a time greater than two weeks.

37. (Original) The composition of claim 22, wherein a therapeutically effect amount of anticancer agent is released from the composition for a time greater than one month.

38. (Original) The composition of claim 22, wherein a therapeutically effect amount of anticancer agent is released from the composition for a time greater than three months.

39. (Original) The composition of claim 22, wherein delivery of the anticancer therapy to the tumor site is sufficient to at least prevent increase of tumor mass without significant weight loss of the mammal.

40. (Previously Presented) The composition of claim 22, wherein delivery of the anticancer therapy to the tumor site is sufficient to promote a decrease in tumor mass without significant weight loss in the mammal.

41. (Original) The composition of claim 22, wherein the particle size of the calcium phosphate is selected to provide a desired release kinetic of the anticancer drug.

42. (Previously Presented) A kit for use in preparing a flowable anticancer composition that remains injectable for at least about 20 minutes, said kit comprising:

(a) dry ingredients comprising a nanocrystalline or poorly crystalline calcium phosphate and a second calcium phosphate in a proportion of about 1:10 to 10:1 by weight;

(b) a physiologically acceptable aqueous lubricant in an amount sufficient to produce a flowable product upon combination with said dry ingredients; and

(c) an anticancer agent in an amount ranging from about 0.01 to 10 wt. % of said dry ingredients.

43. (Original) The kit of claim 42, further comprising a means of mixing the dry ingredients and the lubricant.

44. (Original) The kit of claim 42, further comprising injecting means.